REMARKS

Claims 28-37 are all the claims pending in the application.

Claims 28-30 and 32-37 have been rejected under 35 U.S.C. § 102(b) as anticipated by JP 10-053520 to Nobuyuki et al.

Applicants submit that JP '520 does not disclose or render obvious the subject matter of claims 28-30 and 32-37 and, accordingly, request withdrawal of this rejection

The present invention as set forth in claim 28 is directed to a method for reducing fatigue in animals in the state of fatigue, which comprises administering, to said animals, a fatigue reducing agent comprising reduced coenzyme Q represented by formula (1) of claim 28 as an active ingredient.

The present invention as set forth in claim 29 is directed to a method for reducing fatigue in animals by administering a fatigue reducing agent, and recites that the fatigue reducing agent comprises the reduced coenzyme Q of formula (1) and oxidized coenzyme Q of formula (2).

JP '520 was cited in the previous Office Action. Applicants argued that JP '520 discloses compounds that have a non-branched-chain structure, whereas the reduced coenzyme Q10 of the present application has a branched-chain structure. Applicants maintain that argument.

Thus, JP 10-53520 describes an antifatigue agent containing a compound represented by formula (I) of JP 10-53520, such as idebenone, or a hydroquinone form thereof as an active ingredient. However, C5 in the chemical formula of coenzyme Q10 in the present application has a branched-chain structure, whereas C5 of the compound of JP 10-53520 has a non branched-chain structure (-(CH_2)n). Accordingly, the present invention differs from the invention disclosed in JP 10-53520 since the chemical structures are different.

Further, JP 10-53520 provides no information relating to the antifatigue effect of coenzyme Q10.

The Examiner does not specifically comment on these points. Accordingly, it appears that the Examiner has not understood applicants' arguments.

In order to aid the Examiner in understanding the difference in structure between the non-branched structure of the compounds of JP '520, such as idebenone, and the branched structure of the compounds set forth in the present claims, applicants attach a copy of the first page of WO 2006/100017 and page 9 of this WO '017 document which shows the non-branched chemical structure of idebenone. In addition, applicants attach a copy of the front page and columns 3 and 4 of U.S. Patent 6,184,255 to Mae et al, which is of record in the present application, and which shows the branched structure of the reduced coenzyme Q employed in the present invention.

As can be seen from WO '017, idebenone has a linear alkyl chain without a branch. In contrast, the compound of the present invention has a double bond and a branched-chain.

In addition, oxidized coenzyme Q (ubiquinone) and idebenone are different in the CAS registry number (ubiquinone is 60684-33-5 and idebenone is 58186-27-9).

Thus, the hydroquinone of idebenone in JP10-53520 and the reduced coenzyme Q of the present invention are different compounds.

Since the structure of the reduced coenzyme Q of the present invention is a branched structure and differs from the structure disclosed in JP '520, it is clear that JP '520 does not anticipate the present claims.

In view of the above, applicants submit that JP '520 does not disclose or render obvious the subject matter of claims 28-30 and 32-37 and, accordingly, request withdrawal of this rejection

Claims 28-30 and 32-37 have been rejected under 35 U.S.C. § 102(b) as anticipated by the newly cited South African Patent ZA 2001/09677 to Lehmann.

Applicants submit that ZA 2001/09677 does not disclose or render obvious the subject matter of claims 28-30 and 32-37 and, accordingly, request withdrawal of this rejection.

ZA 2001/09677 discloses the use of a "quinone coenzyme" for improving energy production in a person or animal, for example, in marathon runners, cancer sufferers, sports players, AIDS patients, chronic fatigue syndrome patients and people suffering from stress.

At page 2, line 16 to page 3, line 2, ZA 2001/09677 discloses specific quinone coenzymes. Each of the specific coenzymes disclosed y ZA 2001/09677 are oxidized quinone coenzymes. ZA 2001/09677 does not disclose a reduced quinone coenzyme, and does not disclose a reduced coenzyme Q.

Thus, ZA 2001/09677 does not disclose the use of reduced coenzyme Q as set forth in the present claims.

Further, applicants submit that the superior anti-fatigue effect provided by the reduced coenzyme Q of the present invention is not obvious from ZA 2001/09677, which merely describes ". . . improving energy production in . . . people suffering stress" by the use of oxidized coenzymes.

Applicants note that although the Examiner cites the entire South African patent ZA 2001/09677, the Examiner only sent applicants a Derwent abstract of the patent. The

abstract that the Examiner sent is a 10-page document, and it is not clear that the entire ten pages is an abstract of the South African patent itself. The actual South African patent, a copy of which is enclosed, nowhere refers to "coenzyme Q" compositions, but the 10-page document sent by the Examiner refers to coenzyme Q. The relationship of the discussion of coenzyme Q in the abstract to the actual disclosure of the South African patent is not clear. Applicants request the Examiner to clarify this relationship and identify which portions of the South African patent the Examiner is relying upon. If the abstract sent by the Examiner is considered to be prior art that discloses "coenzyme Q", it is clear that the coenzyme Q would be oxidized coenzyme Q in view of the actual disclosure of the South African patent which only discloses oxidized coenzyme Q and which does not disclose reduced coenzyme Q.

In view of the above, applicants submit that ZA 2001/09677 does not disclose or render obvious the subject matter of claims 28-30 and 32-37 and, accordingly, request withdrawal of this rejection.

Claims 28, 29 and 31 have been rejected under 35 U.S.C. § 102(b) as anticipated by WO 01/85156.

Applicants submit that WO '156 does not disclose or render obvious the subject matter of claims 28-30 and 32-37 and, accordingly, request withdrawal of this rejection

WO '156 was cited in the Information Disclosure Statement filed on November 14, 2006. WO '156 corresponds to US Published Patent Application No. 2005/0070610, a copy of which is attached.

WO '156 also corresponds to Canadian 2406570 that was submitted with the Information Disclosure Statement of July 24, 2008.

WO '156 discloses a method for treatment of skin diseases by applying a composition containing reduced coenzyme Q to a patient suffering from a skin disease. WO '156 does not contain any information about the use of reduced coenzyme Q for reducing fatigue in animals in a state of fatigue. Accordingly, applicants submit that WO '156 does not anticipate the present claims.

In view of the above, applicants submit that WO '156 does not disclose or render obvious the subject matter of claims 28-30 and 32-37 and, accordingly, request withdrawal of this rejection.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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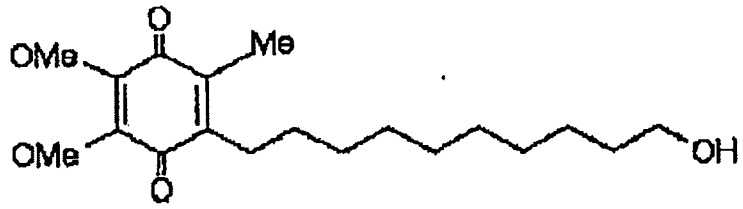
WO 2006/100017 A1

(54) Title: QUINONE DERIVATIVE 2,3-DIMETHOXY-5-METHYL-6-(10-HYDROXYDECYL)-1 ,4- BENZOQUINONE FOR THE TREATMENT OF MUSCULAR DYSTROPHIES

(57) Abstract: Use of idebenone for the preparation of a medicament for the treating of a muscular dystrophy in particular for treating and/or preventing weakness and/or loss of skeletal muscle tissue and/or cardiomyopathy associated with a muscular dystrophy.

(ATP)-producing mitochondrial electron transport chain (ETC). Idebenone has the ability to operate under low oxygen tension situations. Due to its ability to inhibit lipid peroxidation, idebenone protects cell membranes and mitochondria from oxidative damage (Zs.-Nagy I (1990) Chemistry, toxicology, pharmacology and pharmacokinetics of idebenone: a review. Arch. Gerontol. Geriatr. 11:177-186). Its antioxidant properties protect against cerebral ischemia and nerve damage in the central nervous system. Idebenone also interacts with the ETC, preserving ATP formation in ischemic states. This compound is already used as a nootropic drug and has also been shown to stimulate nerve growth factor, a characteristic that could be important in the treatment of Alzheimer's and other neurodegenerative diseases. Idebenone is described in the specification of Japanese Patent Examined Publication No. 3134/1987 filed by Takeda Chemical Industries, Ltd.

Idebenone has the following formula:



2,3-dimethoxy-5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone, Idebenone

Idebenone is preferably administered in dosage ranges form 5 mg/kg/day to 60mg/kg/day, more preferably in a dosage range of 5 mg/kg/day to 40 mg/kg/day and most preferred in a dosage range of 10 mg/kg/day to 30 mg/kg/day.

Further, the idebenone is preferably administered at least one, preferably more times a day, preferably for at least 3 months, more preferably for at least 6 months, most preferably for 6 months to 12 months to observe the initial amelioration of muscle force and improved heart function and normalized heart anatomy. For maintenance of the therapeutic effect prolonged treatment is recommended; the preferred treatment is lifelong.

US006184255B1

(12) **United States Patent**
Mae et al.

(10) **Patent No.: US 6,184,255 B1**
(45) **Date of Patent: Feb. 6, 2001**

(54) **PHARMACEUTICAL COMPOSITION COMPRISING COENZYME Q_{10}**

(75) Inventors: **Tatsumasa Mae**, Kakogawa; **Yoshitomo Sakamoto**, Akashi; **Souichi Morikawa**, Himeji; **Takayoshi Hidaka**, Kobe, all of (JP)

(73) Assignee: **Kaneka Corporation**, Osaka (JP)

(*) Notice: Under 35 U.S.C. 154(b), the term of this patent shall be extended for 0 days.

(21) Appl. No.: **09/242,327**

(22) PCT Filed: **Aug. 18, 1997**

(86) PCT No.: **PCT/JP97/02845**

§ 371 Date: **May 26, 1999**

§ 102(e) Date: **May 26, 1999**

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PCT Pub. Date: **Feb. 26, 1998**

(30) **Foreign Application Priority Data**

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(51) **Int. Cl.**[7] **A61K 31/075**; A01N 31/14
(52) **U.S. Cl.** **514/720**; 514/720; 514/824; 514/878; 514/879
(58) **Field of Search** 514/720, 824, 514/878, 879

(56) **References Cited**

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Weber, C. et al., Molec. Aspects Med., (1994) vol. 15 (Supplement), pp. S97–S102.

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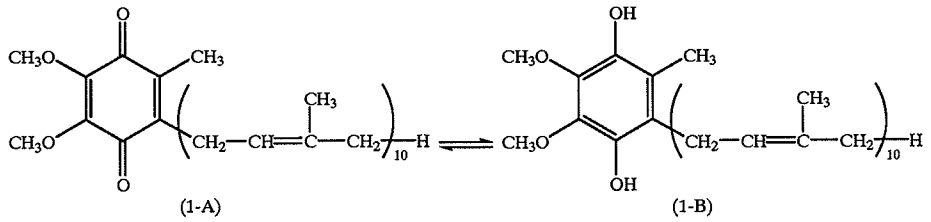
Primary Examiner—Frederick Krass
(74) *Attorney, Agent, or Firm*—Pollock, Vande Sande & Amernick

(57) **ABSTRACT**

The present invention has for its object to provide a medicinal composition comprising coenzyme Q_{10} as an active ingredient, which composition features an enhanced absorption after oral administration. The present invention is directed to a medicinal composition comprising coenzyme Q_{10} as an active ingredient with the reduced form of coenzyme Q_{10} accounting for more than 20 weight % of said coenzyme Q_{10}.

7 Claims, 2 Drawing Sheets

(1)



(1-A) (1-B)

Referring to the above formula (1), the general formula (1-A) represents the oxidized form of coenzyme Q_{10} and the general formula (1-B) represents the reduced form of coenzyme Q_{10}.

In the conventional medicinal composition containing a coenzyme Q_{10} as an active ingredient, the sole active ingredient is the oxidized form of coenzyme Q_{10} of the above chemical formula (1-A). In contrast, the medicinal composition of the present invention comprises a reduced form of coenzyme Q_{10} of the above chemical formula (1-B) as an active ingredient coenzyme Q_{10}. Consequently, as compared with the conventional medicinal composition containing only the oxidized form of coenzyme Q_{10} as an active ingredient, the medicinal composition of the present invention is improved in absorption after oral administration and insures a higher bioavailability.

There is no particular limitation on the technology for providing said reduced form of coenzyme Q_{10}. A typical method, which is by no means exclusive, comprises harvesting a coenzyme Q_{10} from a synthetic reaction mixture, a fermentation broth, or a natural source by procedures known in the art and subjecting it to chromatography to separate and concentrate the reduced form of coenzyme Q_{10} fraction. Where necessary, there can be followed the procedure of adding a conventional reducing agent such as sodium borohydride or sodium dithionite (sodium hydrosulfite) to the above coenzyme Q_{10} to reduce the oxidized form of coenzyme Q_{10} fraction of said coenzyme Q_{10} and, then, concentrate the reduced Q_{10} by chromatography. As a further alternative, the objective reduced form of coenzyme Q_{10} can be obtained by permitting said reducing agent to act on the available high-purity coenzyme Q_{10}.

There is no particular limitation on the technology for manufacturing the medicinal composition of the present invention. A typical but by no means exclusive method comprises dissolving the reduced form of coenzyme Q_{10} thus obtained and a commercial oxidized form of coenzyme Q_{10} in a suitable common solvent such as isopropyl alcohol, acetone, or ether to provide a medicinal composition containing said reduced form of coenzyme Q_{10} in a desired proportion. As an alternative, the above-mentioned reduced and oxidized forms of coenzyme Q_{10} can be simply admixed in solid stage. It is also possible to directly use the mixture of oxidized and reduced forms of coenzyme Q_{10} obtained in the course of the above-mentioned production process for coenzyme Q_{10}. Furthermore, the active ingredient for the medicinal composition of the present invention can be directly obtained by controlling the time of reduction reaction of the high-purity coenzyme Q_{10} already available and the type or amount of reducing agent to be used.

In the medicinal composition of the present invention, the reduced form of coenzyme Q_{10} accounts for more than 20 weight % of the total amount of coenzyme Q_{10}. If its proportion is not less than 20 weight %, the bioavailability of the resulting medicinal composition will not be as high as expected. The preferred proportion is not less than 40 weight % and the most preferred proportion is not less than 60 weight %. Conversely if the proportion of the reduced form of coenzyme Q_{10} is too large, the production process will be complicated and the cost of production increased. Therefore, it is not necessary to increase the coenzyme Q_{10} content too much.

The medicinal composition of the present invention can be used as, for example, a cardiotonic effective against symptoms in ischemic heart disease, senile myocardial sclerosis, hypertensive heart disease, etc. It can also be used as a nutrient, a nutritional supplement, or a veterinary medicine.

There is no particular limitation on the dosage form for the medicinal composition of the present invention. It may for example be powders, granules containing a binder component, or compression-molded tablets. Such powders or granules may be filled in capsule shells to provide capsules. They may also be processed into soft capsules by adding a natural oil, an oily higher fatty acid, a higher fatty acid monoglyceride, or a mixture thereof and wrapping the medicated oil in soft capsule sheet materials. In this application, the capsule shell may be one predominantly composed of gelatin or any other water-soluble macromolecular substance. The capsule includes microcapsules.

The medicinal composition of the present invention may contain, in addition to said reduced form of coenzyme Q_{10}, a variety of pharmaceutically acceptable formulating substances as added in suitable amounts in the routine manner. There is no particular limitation on the kinds of such substances. Thus, an excipient, a disintegrator, a lubricant, a binder, an antioxidant, a coloring agent, an antiflocculant, an absorption promoter, a solubilizer for the active ingredient, a stabilizer, etc. can be added as necessary.

The above-mentioned excipient includes but is not limited to sucrose, lactose, glucose, corn starch, mannitol, crystalline cellulose, calcium phosphate, and calcium sulfate.

The disintegrator includes but is not limited to starch, agar, calcium citrate, calcium carbonate, sodium hydrogen carbonate, dextrin, crystalline cellulose, carboxymethylcellulose, and gum tragacanth.

The lubricant includes but is not limited to talc, magnesium stearate, polyethylene glycol, silica, and hydrogenated vegetable oil.

The binder includes but is not limited to ethylcellulose, methylcellulose, hydroxypropylmethylcellulose, gum tragacanth, shellac, gelatin, gum arabic, polyvinylpyrrolidone, polyvinyl alcohol, polyacrylic acid, polymethacrylic acid, and sorbitol.

The antioxidant includes but is not limited to ascorbic acid, tocopherol, vitamin A, β-carotene, sodium hydrosulfite, sodium thiosulfate, sodium pyrolsulfite, and citric acid.

US 20050070610A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2005/0070610 A1**

Fujii et al. (43) **Pub. Date: Mar. 31, 2005**

(54) **DERMAL COMPOSITIONS CONTAINING COENZYME Q AS THE ACTIVE INGREDIENT**

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(86) PCT No.: **PCT/JP01/03863**

(30) **Foreign Application Priority Data**

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Publication Classification

(51) **Int. Cl.**[7] **A61K 31/12**; A61K 31/075

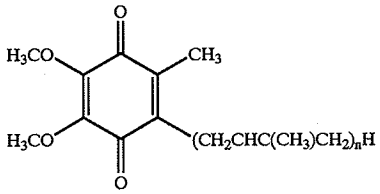
(52) **U.S. Cl.** **514/690**; 514/718

(57) **ABSTRACT**

The present invention provides a composition for dermal application

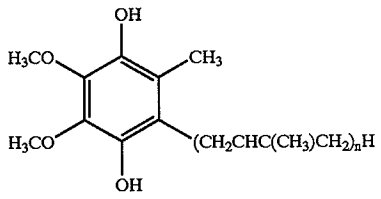
which comprises, as an active ingredient, an oxidized coenzyme Q represented by the formula (1):

(1)



in which n represents an integer of 1 to 12, and/or a reduced coenzyme Q represented by the formula (2):

(2)



in which n represents an integer of 1 to 12, the total content of the oxidized coenzyme Q and reduced coenzyme Q being 0.01 to 99% by weight relative to the whole amount of the composition.

The present invention also provides a therapeutic composition for skin diseases, a cosmetic composition, a skin health care composition and a bath salt composition, each comprising the above composition for dermal application.

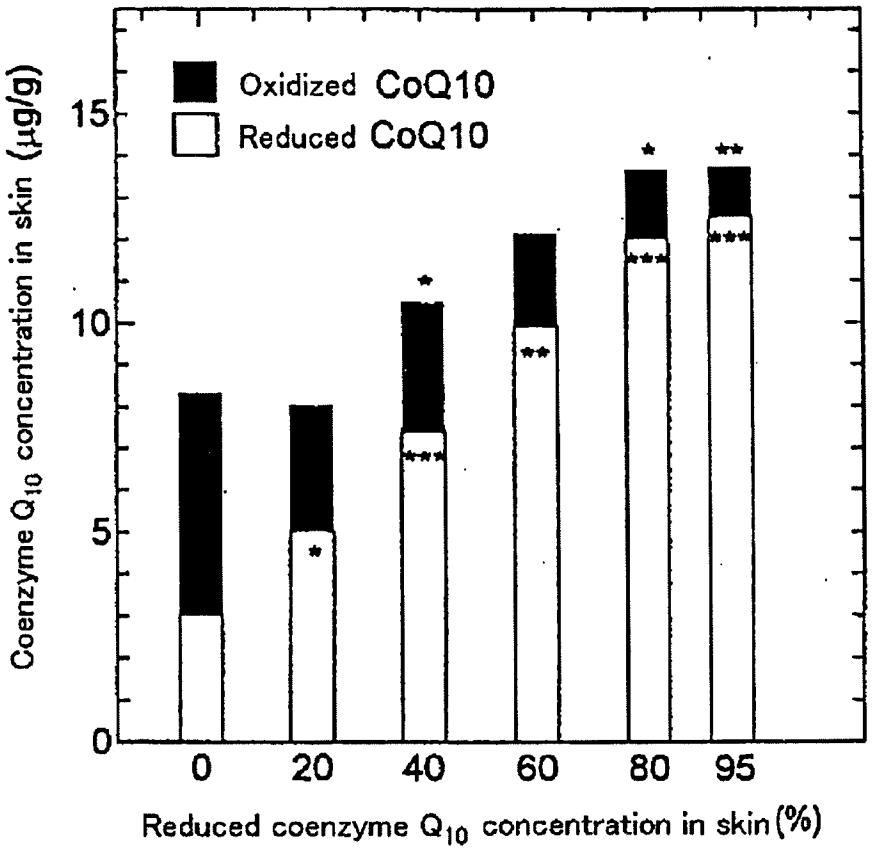
The present invention is further provides a method for the treatment of skin diseases

which comprises applying, to a patient suffering from a skin disease, the above-mentioned therapeutic composition for skin diseases, or

a method for the treatment of skin diseases

which comprises applying, to a patient suffering from a skin disease, the above therapeutic agent for skin diseases other than the oxidized coenzyme Q represented by the formula (1) and other than the reduced coenzyme Q represented by the formula (2) in parallel with a therapeutic composition for skin diseases.

Fig. 1



＊：p＜0．05、＊＊：p＜0．01、＊＊＊：p＜0．001、
in one-tailed Student's t-test

DERMAL COMPOSITIONS CONTAINING COENZYME Q AS THE ACTIVE INGREDIENT

TECHNICAL FIELD

[0001] The present invention relates to a composition for dermal application which contains a coenzyme Q as an active ingredient, in particular to a composition for the treatment of skin diseases, a cosmetic composition, a skin health care composition and a bath salt composition, and to a method for the treatment of skin diseases using that composition for dermal application.

BACKGROUND ART

[0002] Coenzymes Q are physiologically essential factors distributed widely in living organisms, from bacteria to mammals, and occur as constituents of the mitochondrial electron transport system in cells of the living organism. Coenzymes Q function as carrier components in the electron transport system by repeating oxidation and reduction in vivo, and reduced coenzymes Q are also known as antioxidants. In many animals inclusive of human beings, or in fish and birds, coenzyme Q_{10}, which is a coenzyme Q whose side chain comprises 10 repetitions of a unit, is predominant. Further, it is known that about 40 to 90% of this coenzyme Q_{10} occurs in reduced form in living organisms.

[0003] As for the practical uses of coenzymes Q, oxidized coenzyme Q_{10}, for instance, has been used as a drug for congestive heart failure and, in other fields than the pharmaceutical field, it has been used widely as a nutrient or nutritional supplement, like vitamins. However, reduced coenzyme Q_{10} has not yet been put to practical use.

[0004] In Japanese Kohyo Publication Hei-09-501925, there is disclosed a dermal preparation containing oxidized coenzyme Q_{10} (ubiquinone) or reduced coenzyme Q_{10} (ubiquinol) as a coenzyme Q_{10}. In this document, however, it is disclosed only as one of a large number of examples of the active ingredient. As regards ubiquinol, in particular, no example is given for the actual use thereof. It is described that such coenzyme Q_{10}-containing dermal preparations are effective against atopic dermatitis. However, the name of that disease, too, appears only as an example of a large number of skin diseases. There is no relevant example, hence the actual effect is unknown.

[0005] In Japanese Kokai Publication Hei-10-109933, the inventors of the present invention disclosed that the combined use of reduced coenzyme Q_{10} and oxidized coenzyme Q_{10} results in an improvement in oral absorbability as compared with the single use of oxidized coenzyme Q_{10}. However, the effect of reduced coenzymes Q on absorbability upon administration via other routes than the oral or its efficacy in atopic dermatitis was quite unknown.

[0006] It is a problem that skin diseases exert great influences on the life of patients not only physically but also mentally. In particular, the number of patients suffering from the intractable skin disease atopic dermatitis, among others, is tremendous and, further, the number of adult patients with atopic dermatitis has been increasing in recent years, causing serious problems in their leading a social life.

[0007] Steroids are generally known as therapeutic agents for atopic dermatitis. However, their use is restricted in not a few instances because of their significant side effects and the possibility of their causing the rebound phenomenon. Therefore, they are not sufficiently effective agents to bring about complete recovery from atopic dermatitis. Furthermore, in cases where steroids are ineffective, there are, in fact, no therapeutic drugs available. It is also a social problem that there are victims of folk medicine.

[0008] Tacrolimus, which is an immunosuppressive, has recently been approved as a therapeutic agent for atopic dermatitis. However, its use in children has not yet been approved because of a strong fear of its producing side effects; thus, it cannot be said to be a safe agent.

[0009] Under such circumstances, the advent of a therapeutic agent that can be used safely against atopic dermatitis is earnestly demanded.

SUMMARY OF THE INVENTION

[0010] It is an object of the present invention to provide a composition for dermal application which contains coenzyme Q, in particular coenzyme Q_{10}, as an active ingredient, and thus provide a safe and highly effective therapeutic agent for skin diseases, in particular atopic dermatitis.

[0011] As a result of investigations made by the present inventors to solve the problems mentioned above, it was found that oxidized coenzyme Q_{10} can produce an excellent therapeutic effect on atopic dermatitis. Surprisingly, it was also found that when oxidized coenzyme Q_{10} is used in combination with an existing drug such as a steroid or tacrolimus, a synergistic effect, which is higher as compared with the single use of such an existing drug, can be obtained.

[0012] Further, the inventors of the present invention prepared a dermal preparation containing reduced coenzyme Q_{10} and carried out a percutaneous absorption test, whereupon it was found that when a composition containing a certain proportion of reduced coenzyme Q_{10} as coenzyme Q_{10} is applied to the skin, a higher level of percutaneous absorption can be attained as compared with a composition containing oxidized coenzyme Q_{10} alone and the amount of coenzyme Q_{10} in the skin can be much increased. Furthermore, it was surprisingly found that the content of reduced coenzyme Q_{10}, which is the active principle showing antioxidant activity, in skin can be markedly increased by applying a composition containing reduced coenzyme Q_{10} as compared with the application of oxidized coenzyme Q_{10} alone. Heretofore, it has been considered that oxidized coenzyme Q_{10}, when administered, is converted to the reduced form in vivo and thus can show antioxidant activity. However, our studies revealed that the reduction of oxidized coenzyme Q_{10} in skin proceeds only very slowly and, therefore, the reduced form level is far inferior to that attainable by application of a composition containing reduced coenzyme Q_{10}. By increasing the content in skin of reduced coenzyme Q_{10}, which shows strong antioxidant activity, it becomes possible to expect higher levels of skin care activity as compared with the application of oxidized coenzyme Q_{10} alone.

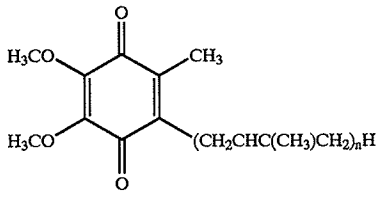
[0013] Further, the inventor of the present invention evaluated an ointment containing reduced coenzyme Q_{10} for efficacy in the treatment of atopic dermatitis. As a result, it was found that a reduced coenzyme Q_{10}-containing ointment is by itself highly effective and comparable in therapeutic effect to prednisolone. It was also found that when a

reduced coenzyme Q_{10}-containing ointment is used in combination with a steroid or tacrolimus, a more powerful therapeutic effect can be produced.

[0014] Furthermore, the inventor of the present invention found that such dermal preparation containing coenzyme Q_{10} as main active ingredient has a skin restoration promoting activity. This suggests that coenzyme Q_{10} be effective also against skin diseases, typically decubitus.

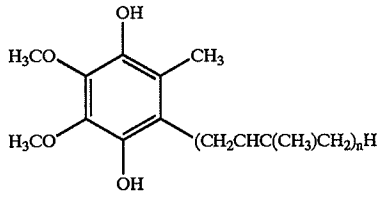
[0015] Thus, the present invention provides a composition for dermal application which comprises, as an active ingredient, an oxidized coenzyme Q represented by the formula (1):

(1)



[0016] wherein n represents an integer of 1 to 12, and/or a reduced coenzyme Q represented by the formula (2):

(2)



[0017] wherein n represents an integer of 1 to 12, the total content of the oxidized coenzyme Q and reduced coenzyme Q being 0.01 to 99% by weight relative to the whole amount of the composition.

[0018] The present invention also relates to a therapeutic composition for skin diseases, a cosmetic composition, a skin health care composition and a bath salt composition, each comprising the above composition for dermal application.

[0019] The present invention is further concerned with a method for the treatment of skin diseases

[0020] which comprises applying, to a patient suffering from a skin disease, the above-mentioned therapeutic composition for skin diseases, or

[0021] a method for the treatment of skin diseases

[0022] which comprises applying, to a patient suffering from a skin disease, the a therapeutic agent for skin diseases other than the oxidized coenzyme Q represented by the formula (1) and other than the reduced coenzyme Q represented by the formula (2) in parallel with above-mentioned therapeutic composition for skin diseases.

[0023] In the following, the present invention is described in detail.

DETAILED DISCLOSURE OF THE INVENTION

[0024] The compounds represented by the above formula (1) are oxidized coenzymes Q, while the compounds represented by the above formula (2) are reduced coenzymes Q.

[0025] The method of obtaining oxidized coenzymes Q and reduced coenzymes Q is not particularly restricted but the coenzymes Q can be obtained in the conventional manner, for example by synthesis, fermentation, or extraction from natural sources. Or, also employable is a method comprising, for example, subjecting the product obtained in the above manner to chromatography and concentrating the oxidized coenzyme Q fraction or reduced coenzyme Q fraction in an eluate. The oxidized form of coenzyme Q can be obtained by a method known in the art. The reduced from of coenzyme Q may be obtained by adding a conventional reducing agent, such as sodium borohydride or sodium dithionite (sodium hydrosulfite), as necessary, to the above coenzyme Q and reducing the oxidized form of coenzyme Q contained in the above coenzyme Q to the reduced form of coenzyme Q in a conventional manner, followed by concentration by chromatography. It is also possible to obtain the reduced form of coenzyme Q by treating an existing highly pure coenzyme Q with such as a reducing agent as mentioned above.

[0026] The method of obtaining the composition of the present invention is not particularly restricted but the composition can be obtained, for example, by dissolving the reduced form of coenzyme Q obtained in the above manner and the oxidized form of coenzyme Q, which is commercially available or obtained by a method known in the art, either in admixture or individually, in an appropriate base. Alternatively, the mixture of reduced coenzyme Q and oxidized coenzyme Q as obtained in the above-mentioned process for coenzyme Q production may be dissolved as such in a base. The base may be selected according to need from among those conventionally used in pharmaceutical preparations, cosmetics and the like within the limits within which the effects of the present invention will not be lessened.

[0027] In the composition of the present invention, the total proportion of the oxidized coenzyme Q and reduced coenzyme Q relative to the whole amount of the composition (proportion of the oxidized coenzyme Q relative to the whole composition when the oxidized coenzyme Q alone is contained therein, or proportion of the reduced coenzyme Q relative to the whole composition when the reduced coenzyme Q alone is contained therein) is 0.01 to 99% by weight, preferably 0.1 to 95% by weight, more preferably 0.5 to 50% by weight, still more preferably 1 to 30% by weight.

[0028] From the percutaneous absorbability viewpoint, the proportion of the reduced coenzyme Q relative to the total amount of the oxidized coenzyme Q and reduced coenzyme Q is preferably not less than 20% by weight, more preferably not less than 40% by weight. However, a reduced coenzyme Q-free composition containing only the oxidized coenzyme Q can also be preferably used. Further, the proportion of the reduced coenzyme Q relative to the total amount of the oxidized coenzyme Q and reduced coenzyme Q is preferably not more than 95% by weight.

[0029] The oxidized coenzyme Q and reduced coenzyme Q which can be used in the practice of the present invention have a side chain in which, as shown by the above formulas (1) and (2), the number (n in each formula) of repetitions of the repeating unit is 1 to 12. Among them, those in which the number of repetitions of the repeating unit is 10, namely oxidized coenzyme Q_{10} and reduced coenzyme Q_{10}, are particularly preferred.

[0030] The above composition for dermal application, therapeutic composition for skin diseases, cosmetic composition, skin health care composition and bath salt composition may be intended for application to humans or for application to pets, domestic animals and/or birds, in particular dogs and/or cats.

[0031] The dosage form of the dermal composition of the present invention is not particularly restricted but includes, among others, cream-like, paste-like, jelly-like, gel-like, emulsion-like or liquid dosage forms prepared by dissolving or dispersing together the above agent(s) in appropriate bases (ointments, liniments, lotions, sprays, etc.), dosage forms prepared by spreading a solution or dispersion of the above agent(s) in a base onto supporting members (poultices etc.), and dosage forms prepared by spreading a solution or dispersion of the above agent(s) in a pressure sensitive adhesive composition onto supporting members (plasters, tapes, etc.).

[0032] The dermal composition of the present invention can be used as a therapeutic composition for skin diseases. The skin diseases which can be treated with the composition include, but are not limited to, atopic dermatitis, decubitus, wounds, burns, psoriasis, eruptions, contact dermatitis, seborrheic dermatitis, lichen simplex chronicus Vidal, nummular eczema, housewives' eczema, solar dermatitis, pruritus cutaneus, prurigo Devergie, drug eruption, lichen planus, pityriasis rubra pilaris, pityriasis rosea Gibert, erythema, erythrodermia, wounds, athlete's foot, and skin ulcer, among others.

[0033] In using the dermal composition of the present invention as a therapeutic composition for skin diseases, the composition may further contain a substance showing antioxidant activity, for example superoxide dismutase, catalase, glutathione peroxidase, vitamin E, vitamin C, glutathione, glutathione reductase, a polyvalent unsaturated fatty acid or the like. It may also contain a skin activating ingredient, for example collagen, hyaluronic acid, mutin, a ceramide, squalene, squalane or the like, or a percutaneous absorption promoter.

[0034] It may further contain a therapeutic ingredient for skin diseases other than the oxidized coenzyme Q and reduced coenzyme Q. As such ingredient, there may be mentioned those drugs which are generally used in the area of dermatological treatment, for example anti-inflammatory agents, immunosuppressives, antibacterial substances, antifungal agents, and disinfectants and, further, such antioxidant substances or skin activating ingredients as mentioned above.

[0035] When the therapeutic composition for skin diseases according to the invention is intended for use in the treatment of atopic dermatitis, it preferably further contains a therapeutic agent for atopic dermatitis other than the oxidized coenzyme Q and reduced coenzyme Q. Such therapeutic agent for atopic dermatitis may be any of those generally used in the treatment of atopic dermatitis, including steroids, more specifically prednisolone valerate acetate, amcinonide, diflucortolone valerate, dexamethasone valerate, clobetasol propionate, diflorasone diacetate, dexamethasone propionate, betamethasone dipropionate, difluprednate, fluocinonide, halcinonido, budesonide, hydrocortisone butyrate propionate, betamethasone valerate, beclomethasone dipropionate, fluocinolone acetonide, triamcinolone acetonide, flumethasone pivalate, hydrocortisone butyrate, clobetasone butyrate, alclometasone dipropionate, dexamethasone, methylprednisolone acetate, prednisolone, and hydrocortisone acetate, and other drugs than steroids, for example tacrolimus, and antihistamines.

[0036] The dermal composition of the present invention can be used as a cosmetic composition or a skin health care composition. Specific uses include, but are not limited to, cleansers, eye creams, eyeshadows, creams, milky lotions, skin lotions, perfumes, face powders, cosmeticoils, paste perfumes, powders, packs, shaving creams, shaving lotions, suntan oils, anti-suntan oils, suntan lotions, anti-suntan lotions, nail creams, nail enamels, bath cosmetics, rouge, mascara, lipsticks, lip creams, eyeliners, deodorants, cologne waters, etc.

[0037] In this case, the above composition may contain one or more of those cosmetic auxiliaries so far used in the conventional cosmetic or skin health care compositions, for example preservatives, bactericides, perfumes, antifoaming agents, colorants, coloring pigments, thickeners, surfactants, emulsifiers, softening agents, moistening agents and/or humectants, fats, oils, waxes and, further, alcohols, polyols, polymers, foam stabilizers, electrolytes, organic solvents, silicone derivatives, and other ingredients.

[0038] The dermal composition of the present invention can be used also as a bath salt or like composition. The bath salt or like composition so referred to herein means a composition to be dissolved in cold or warm water for use thereof at the time of bathing. The bath salt or like composition of the present invention may comprise additive and other ingredients conventionally used in bath salt preparations.

BRIEF DESCRIPTION OF THE DRAWING

[0039] **FIG. 1** is a graphic representation of the relationship between the concentration of coenzyme Q_{10} in skin and the content of reduced coenzyme Q_{10} in sample. The vertical axis denotes the total concentration of coenzyme Q_{10} in skin, and the horizontal axis denotes the content of reduced coenzyme Q_{10} in coenzyme Q_{10} in the sample applied. Each bar represents the mean±standard deviation (n=4 or 5).

BEST MODES FOR CARRYING OUT THE INVENTION

[0040] The following examples and preparation examples illustrate the present invention in more detail. They are, however, by no means limitative of the scope of the present invention.

EXAMPLE 1

[0041] (1) Preparation of Test Sample 1

[0042] Reduced coenzyme Q_{10} (0.1 g; containing about 5% of oxidized coenzyme Q_{10}) was melted on a water bath

at 50° C. Thereto was added polyethylene glycol 1500 (PEG 1500) melted in the same manner to make a total amount of 10 ml. This was made homogeneous by melting and mixing at 50° C. and then allowed to solidify at room temperature to give an ointment-like composition.

[0043] (2) Preparation of Comparative Sample 1

[0044] Oxidized coenzyme Q_{10} (0.1 g) was melted on a water bath at 50° C. Thereto was added PEG 1500 to make a total amount of 10 ml. This was made homogeneous by melting and mixing at 50° C. and then allowed to solidify at room temperature to give an ointment-like composition.

[0045] (3) Percutaneous Absorption Test

[0046] The test sample 1 and comparative sample 1 were used as test substances. The test was carried out using male hairless rats (weighing 250 to 300 g) fed under well-fed conditions. A 0.1-g portion of the test sample 1, comparative sample 1, or PEG 1500 as a control was applied to an area of 3 cm square on the back of each hairless rat lightly anesthetized with ether. Three hours, 8 hours or 24 hours after application, the rat was sacrificed by euthanasia, the applied area was washed thoroughly, and a skin sample was taken. The skin sample was homogenized and extracted with propanol, the extract was concentrated using a solid phase column, and the amount of coenzyme Q_{10} in the skin was determined by high-performance liquid chromatography. The total amount of coenzyme Q_{10} in each skin sample is shown in Table 1. The numerical value shows the mean value±standard deviation.

TABLE 1

	Coenzyme Q_{10} concentration in skin (μg/g)		
	3 hr	8 hr	24 hr
Control (PEG 1500)	1.51 ± 0.38	1.35 ± 0.39	1.62 ± 0.50
Oxidized coenzyme Q_{10}	8.32 ± 1.35 (100)	7.87 ± 1.75 (100)	7.63 ± 2.69 (100)
Reduced coenzyme Q_{10} #1	13.72 ± 0.70 (165***)	17.96 ± 4.85 (228*)	15.68 ± 3.95 (206*)

Mean ± SD, n = 3 to 8.
*p < 0.05, ***p < 0.001, in one-tailed Student's t-test.
#1Containing about 5% of oxidized coenzyme Q_{10}.

[0047] As shown above, it was revealed that the coenzyme Q_{10} containing 95% of reduced coenzyme Q_{10} is very effective in increasing the amount of coenzyme Q_{10} in skin as compared with 100% oxidized coenzyme Q_{10}.

[0048] Each of the skin samples mentioned above was homogenized and extracted with hexane, the extract was evaporated to dryness and dissolved in ethanol, and the proportion of reduced coenzyme Q_{10} in skin was determined by high-performance liquid chromatography with an electrochemical detector. The amounts of reduced coenzyme Q_{10} in skin thus found are shown in Table 2. Each numerical value means the mean±standard deviation.

TABLE 2

	Reduced coenzyme Q_{10} concentration in skin (μg/g)		
	3 hr	8 hr	24 hr
Control (PEG 1500)	1.11 ± 0.26	0.84 ± 0.23	1.13 ± 0.39
Oxidized coenzyme Q_{10}	3.02 ± 1.22 (100)	4.99 ± 2.12 (100)	5.44 ± 2.36 (100)
Reduced coenzyme Q_{10} #1	12.55 ± 0.51 (414***)	15.84 ± 4.56 (317**)	12.99 ± 4.81 (239*)

Mean ± SD, n = 3 to 8.
*p < 0.05, **p < 0.01, ***p < 0.001, in one-tailed Student's t-test.
#1Containing about 5% of oxidized coenzyme Q_{10}.

[0049] As shown above, it was revealed that the coenzyme Q_{10} containing 95% of reduced coenzyme Q_{10} is very effective in increasing the amount of reduced coenzyme Q_{10} in skin as compared with 100% oxidized coenzyme Q_{10}. Although the amount of reduced coenzyme Q_{10} in skin is gradually increased by the reduction of oxidized coenzyme Q_{10} in the treated skin, the rate thereof is not very rapid. Even after 24 hours after application of oxidized coenzyme Q_{10}, the amount of reduced coenzyme Q_{10} in skin is only half or less as compared with the level 3 hours after application of reduced coenzyme Q_{10}.

EXAMPLE 2

[0050] (1) Preparation of Test Sample 2

[0051] The sample was prepared in the same manner as described above in Example 1 for test sample 1 except that a mixture of oxidized coenzyme Q_{10} and reduced coenzyme Q_{10} in a mixing ratio of 80:20 by weight was used.

[0052] (2) Preparation of Test Sample 3

[0053] The sample was prepared in the same manner as described above in Example 1 for test sample 1 except that a mixture of oxidized coenzyme Q_{10} and reduced coenzyme Q_{10} in a mixing ratio of 60:40 by weight was used.

[0054] (3) Preparation of Test Sample 4

[0055] The sample was prepared in the same manner as described above in Example 1 for test sample 1 except that a mixture of oxidized coenzyme Q_{10} and reduced coenzyme Q_{10} in a mixing ratio of 40:60 by weight was used.

[0056] (4) Preparation of Test Sample 5

[0057] The sample was prepared in the same manner as described above in Example 1 for test sample 1 except that a mixture of oxidized coenzyme Q_{10} and reduced coenzyme Q_{10} in a mixing ratio of 20:80 by weight was used.

[0058] (5) Percutaneous Absorption Test

[0059] The test was carried out in the same manner as in Example 1 using the test samples 2, 3, 4 and 5 as well as the comparative sample 1 as test samples.

[0060] The results of the test are shown in **FIG. 1**. In **FIG. 1**, the vertical axis denotes the total amount of coenzyme Q_{10} and the amount of reduced coenzyme Q_{10} in skin at 3 hours after application, and the horizontal axis denotes the content (% by weight) of reduced coenzyme Q_{10} relative to the total amount of coenzyme Q_{10} in the sample applied. Each bar indicates the mean value.

[0061] As is evident from **FIG. 1**, the composition in which the proportion of reduced coenzyme Q_{10} was 20% by weight gave a significantly increased concentration of reduced coenzyme Q_{10} in skin as compared with the composition comprising oxidized coenzyme Q_{10} alone. Further, with the composition containing reduced coenzyme Q_{10} in a proportion of 40% by weight, a still higher concentration was observed as compared with the composition containing reduced coenzyme Q_{10} in a proportion of 20% by weight. From these results, it was revealed that when it contains not less than 20% by weight of reduced coenzyme Q_{10}, the composition of the present invention can undoubtedly increase the amount of reduced coenzyme Q_{10} in skin as compared with the composition containing oxidized coenzyme Q_{10} alone or the composition containing less than 20% by weight of reduced coenzyme Q_{10} relative to the total amount of coenzyme Q_{10}.

EXAMPLE 3

[0062] Therapeutic Effect in Atopic Dermatitis Model Mice (NC Mice) -1

[0063] The method of Hirasawa et al. (Oyo Yakuri (Applied Pharmacology), Vol. 59, No. 6, pp. 123-134, 2000) was used for the evaluation. Ointments containing oxidized coenzyme Q_{10} and ointments containing reduced coenzyme Q_{10} (containing 5% of oxidized coenzyme Q_{10} in coenzyme Q_{10}) were evaluated for therapeutic effect in atopic dermatitis model mice (NC mice) Dermatitis was induced in each group of 7 NC mice by sensitizing (once a week) using a hapten. On the occasion of the third sensitization, the treatment with each test compound was started. The coenzyme Q_{10}-containing ointment (1%) was applied at a dose of 0.1 g every day, while the positive control prednisolone ointment was applied once every other day. In the group in which the prednisolone ointment and the coenzyme Q_{10} ointment were used combinedly, the ointments were applied alternately. The therapeutic effect was evaluated on a scoring scale of 0 to 3 (0: no symptom, 1: slight, 2: medium, 3: severe) for the 5 items: 1-pruritus, 2-rubefaction, bleeding, 3-edema, 4-abrasion, tissue deficit, 5-crusting, dryness. The differences between the dermatitis scores at the start of the test and those on day 15 after the start of application are shown in Table 3. Each data indicates the mean±standard deviation.

TABLE 3

Test group	Increase in dermatitis score
Control group	4.4 ± 1.18 (100)
1% Oxidized coenzyme Q_{10} ointment	3.3 ± 2.14 (75)
1% Reduced coenzyme Q_{10} ointment*	3.1 ± 2.04 (70)
Prednisolone ointment (P)	2.1 ± 1.35 (48)
Prednisolone ointment (P)	2.1 ± 1.35 (100)
P + 1% oxidized coenzyme Q_{10} ointment	1.1 ± 1.07 (52)
P + 1% reduced coenzyme Q_{10} ointment*	−1.3 ± 1.98 (—)

Mean ± SD, n = 7
*Total coenzyme Q_{10} contained about 5% of oxidized coenzyme Q_{10}.

[0064] A greater score value indicates a higher level of aggravation of dermatitis during testing. In the oxidized, and reduced coenzyme Q_{10} ointment groups, the ointments showed an obvious aggravation preventing effect, like in the positive control prednisolone ointment, as compared with the control group. In the group of combined use with prednisolone, a more powerful therapeutic effect was shown as compared with the group of single use of prednisolone, and the reduced coenzyme Q_{10} ointment, in particular, gave a score lower than the score at the start of testing, indicating its dermatitis healing ability. It has so far been quite unknown in the art that ointments containing a coenzyme Q as its main active ingredient is actually effective against atopic dermatitis in the manner mentioned above. Furthermore, it has never been anticipated that when used combinedly with a steroid, a coenzyme Q can show such a more potent effect.

EXAMPLE 4

[0065] Therapeutic Effect in Atopic Dermatitis Model Mice (NC Mice) -2

[0066] The effect of the single use of a high concentration coenzyme Q_{10} ointment (10%) and the effect of the combined use of Protopic ointment (tacrolimus preparation), a therapeutic agent for atopic dermatitis, and a low concentration coenzyme Q_{10} ointment (1%) were examined by carrying out the same test as in Example 3. In the single use evaluation group, the test ointment was applied every day and, in the combined use evaluation group, Protopic ointment was applied at a does of 0.1 g once a week and 0.1 g of the low concentration coenzyme Q_{10} ointment on the remaining 6 days per week. In a control group, Protopic ointment was applied singly 6 times a week. In a positive control group, a prednisolone ointment was applied every other day. The results obtained on the 15th day after commencement of application are shown in Table 4. Each value indicates the mean±standard deviation.

TABLE 4

Test group	Increase in dermatitis score
Control group	4.1 ± 0.90 (100)
10% Oxidized coenzyme Q_{10} ointment	4.0 ± 1.53 (98)
10% Reduced coenzyme Q_{10} ointment*	2.9 ± 1.21 (71)
Prednisolone ointment (P)	2.7 ± 2.14 (66)
Protopic ointment (P)	5.4 ± 1.90 (100)
P + 1% oxidized coenzyme Q_{10} ointment	3.7 ± 1.80 (69)
P + 1% reduced coenzyme Q_{10} ointment*	3.0 ± 1.73 (56)

Mean ± SD, n = 7
*Total coenzyme Q_{10} contained about 5% of oxidized coenzyme Q_{10}.

[0067] The high-concentration reduced coenzyme Q_{10} ointment was roughly comparable in therapeutic effect to the positive control prednisolone ointment, indicating that it can show a potent therapeutic effect even when used singly. On the other hand, Protopic ointment in the single use group showed no efficacy probably due to the small number of applications. However, when Protopic ointment was used in combination with the low concentration coenzyme Q_{10} ointment, a distinct synergistic effect was shown and aggravation was suppressed. That the coenzyme Q_{10} ointments used combinedly with tacrolimus also showed a synergistic effect like in the combined use with the steroid preparation indicates that the synergistic effect of the coenzyme Q_{10} ointment on atopic dermatitis is not specific to the steroid preparation.

EXAMPLE 5

[0068] Incised Wound Healing Test in Rats

[0069] SD rats (male, 12-week-old) were clipped of hairs and divided into groups of 10 animals to make the mean body weights of the groups roughly the same, and subjected to the test. Each animal was given an incision wound along the median line under diethyl ether anesthesia. The incision wound was stapled at three sites using Michel's clips, and a 1% oxidized coenzyme Q_{10} ointment or a 1% reduced coenzyme Q_{10} ointment was applied at a dose of 0.2 g/day for 4 days. Two control groups, namely a nontreated group and an ointment base group treated with the same dose of the ointment base, were used. Three days after incision, the Michel's clips were removed and, four days after incision, each animal was euthanized by overanesthesia with diethyl ether, the skin around the incision was peeled off, and skin sections were prepared. The skin sections were measured for tension on a tensile tester.

[0070] As a result, it was noted that oxidized coenzyme Q_{10} and reduced coenzyme Q_{10} have a skin repair promoting effect.

EXAMPLE 6

[0071] Oxidation Stability Evaluation of Reduced Coenzyme Q_{10} in Ointment

[0072] Reduced coenzyme Q_{10}-containing ointments were evaluated for oxidation stability. The ointment bases used were PEG 1500, a hydrophilic ointment, an absorptive ointment, and a simple ointment. The PEG 1500 used was a product of Wako Pure Chemical Industries, and the hydrophilic ointment, absorptive ointment and simple ointment used were respectively the products according to the Japanese Pharmacopoeia. Using the respective bases and reduced coenzyme Q_{10}, ointments were prepared in the same manner as in Example 1. The thus-prepared reduced coenzyme Q_{10} ointments were stored at 23° C. for 2 weeks either in air or in a vessel purged with nitrogen, and the proportion of the reduced form of coenzyme Q_{10} in each ointment was determined by HPLC. The results thus obtained are shown in Table 5.

TABLE 5

Base	Concentration (%)*1	Proportion of reduced coenzyme Q_{10} (%)*2 4° C. in air	23° C. in air	23° C. in nitrogen
PEG1500	1	87.5	56.4	62.3
PEG1500	10	92.5	94.4	93.6
Hydrophilic ointment	1	—	75.1	79.3
Absorptive ointment	1	—	29.8	5.3
Simple ointment	1	—	83.9	83.6
Mean, n = 2				

*1Concentration of coenzyme Q_{10} in ointment

*2Proportion of reduced coenzyme Q_{10} in total coenzyme Q_{10} in ointment after 2 weeks of storage under respective conditions.

—Not tested.

[0073] In the reduced coenzyme Q_{10} ointments prepared by using simple ointment and hydrophilic ointment, respectively, as bases, about 80% of coenzyme Q_{10} retained the reduced form after the 2 weeks of storage whereas, in the PEG 1500-based and absorptive ointment-based ointments, only 60% and 30%, respectively, of the reduced form remained. As regards the oxidation stability of reduced coenzyme Q_{10} in the ointments, the substitution of the storage vessel atmosphere with nitrogen showed no protective effect. When the PEG 1500-based ointment was stored at 4° C. in a refrigerator, the enzyme stability was assured for 2 weeks. Evaluation of the dependency on the concentration of reduced coenzyme Q_{10} in ointment revealed that the 10% ointment is higher in stability than the 1% preparation, namely the higher the concentration is, the more stable the preparation is.

PREPARATION EXAMPLE 1

[0074] A coenzyme Q_{10}-containing hydrophilic ointment was prepared by a conventional method according to the following formulation.

Hydrophilic ointment	99.000% by weight
coenzyme Q_{10}	1.000% by weight

PREPARATION EXAMPLE 2

[0075] A coenzyme Q_{10}-containing W/O cream was prepared by a conventional method according to the following formulation.

Glycerol sorbitan fatty acid ester	6.000% by weight
Microcrystalline wax	1.000% by weight
Olive oil	3.000% by weight
Liquid paraffin	19.000% by weight
Magnesium stearate	1.000% by weight
Propylene glycol	3.700% by weight
Magnesium sulfate ($MgSO_4.7H_2O$)	0.700% by weight
Coenzyme Q_{10}	1.000% by weight
Dehydrated salt to make	100.000% by weight

PREPARATION EXAMPLE 3

[0076] A coenzyme Q_{10}-containing W/O emulsion was prepared by a conventional method according to the following formulation.

Polyoxyethylene glycerol sorbitan fatty acid ester	3.600% by weight
Polyoxyethylene fatty acid ester	1.400% by weight
Cetearyl alcohol	2.000% by weight
Mineral oil, GP 9	20.000% by weight
Paraben mixture	q.v.
Magnesium sulfate ($MgSO_4.7H_2O$)	0.700% by weight
Coenzyme Q_{10}	1.000% by weight
Calcium chloride ($CaCl_2$)	0.85% by weight
Dehydrated salt to make	100.000% by weight

PREPARATION EXAMPLE 4

[0077] A coenzyme Q_{10}-containing W/O lotion was prepared by a conventional method according to the following formulation.

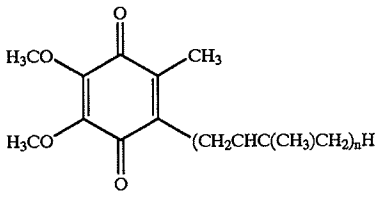
Glycerol sorbitan fatty acid ester	1.300% by weight
Polyoxyethylene fatty acid ester	3.700% by weight
Neutral oil	6.000% by weight
Liquid paraffin, GP 9	14.000% by weight
Propylene glycol	3.800% by weight
Magnesium sulfate ($MgSO_4.7H_2O$)	0.700% by weight
Ribonic acid	1.500% by weight
Coenzyme Q_{10}	1.000% by weight
Desalted water to make	100.000% by weight

INDUSTRIAL APPLICABILITY

[0078] The composition of the present invention, which has the above constitution, is excellent in percutaneous absorption of coenzyme Q_{10} and highly effective in the treatment of skin diseases, such as atopic dermatitis, and in skin health care.

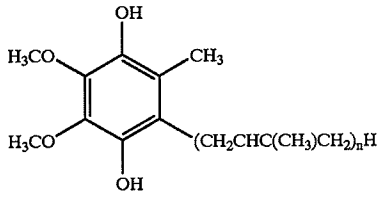
1. A composition for dermal application which comprises, as an active ingredient, an oxidized coenzyme Q represented by the formula (1):

(1)



in which n represents an integer of 1 to 12, and/or a reduced coenzyme Q represented by the formula (2):

(2)



in which n represents an integer of 1 to 12,

the total content of the oxidized coenzyme Q and reduced coenzyme Q being 0.01 to 99% by weight relative to the whole amount of the composition.

2. The composition for dermal application according to claim 1,

wherein the proportion of the reduced coenzyme Q relative to the total amount of the oxidized coenzyme Q represented by the formula (1) and the reduced coenzyme Q represented by the formula (2) is not less than 20% by weight.

3. The composition for dermal application according to claim 2,

wherein the proportion of the reduced coenzyme Q relative to the total amount of the oxidized coenzyme Q represented by the formula (1) and the reduced coenzyme Q represented by the formula (2) is not less than 40% by weight.

4. The composition for dermal application according to any of claims 1 to 3,

wherein the proportion of the reduced coenzyme Q relative to the total amount of the oxidized coenzyme Q represented by the formula (1) and the reduced coenzyme Q represented by the formula (2) is not more than 95% by weight.

5. The composition for dermal application according to claim 1,

which does not contain any of the reduced coenzymes Q represented by the formula (2) but contains an oxidized coenzyme Q represented by the formula (1).

6. The composition for dermal application according to any of claims 1 to 5,

wherein the oxidized coenzyme Q represented by the general formula (1) is oxidized coenzyme Q_{10} and the reduced coenzyme Q represented by the general formula (2) is reduced coenzyme Q_{10}.

7. The composition for dermal application according to any of claims 1 to 6,

which is to be applied to a human.

8. The composition for dermal application according to any of claims 1 to 6,

which is to be applied to pets, a domestic animal and/or a bird.

9. The composition for dermal application according to claim 8,

which is to be applied to a dog and/or a cat.

10. A therapeutic composition for skin diseases which comprises the composition for dermal application according to any of claims 1 to 9.

11. The therapeutic composition for skin diseases according to claim 10,

which is to be used for the treatment of at least one skin disease selected from the group consisting of atopic dermatitis, decubitus, wounds, burns, psoriasis, eruptions, contact dermatitis, seborrheic dermatitis, lichen simplex chronicus Vidal, nummular eczema, housewives' eczema, solar dermatitis, pruritus cutaneus, prurigo, drug eruption, lichen planus, pityriasis rubra pilaris Devergie, pityriasis rosea Gibert, erythema, erythrodermia, wounds, athlete's foot, and skin ulcer.

12. The therapeutic composition for skin diseases according to claim 10 or 11,

which further comprises a therapeutic ingredient for skin diseases other than the oxidized coenzyme Q represented by the formula (1) and other than the reduced coenzyme Q represented by the formula (2).

13. The therapeutic composition for skin diseases according to claim 12,

wherein the therapeutic ingredient for skin diseases other than the oxidized coenzyme Q represented by the formula (1) and other than the reduced coenzyme Q represented by the formula (2) is a therapeutic agent for atopic dermatitis other than the oxidized coenzyme Q represented by the formula (1) and other than the reduced coenzyme Q represented by the formula (2).

14. The therapeutic composition for skin diseases according to claim 13,

wherein the therapeutic agent for atopic dermatitis other than the oxidized coenzyme Q represented by the formula (1) and other than the reduced coenzyme Q represented by the formula (2) is a steroid or tacrolimus.

15. A cosmetic composition

which comprises the composition for dermal application according to any of claims 1 to 9.

16. A skin health care composition

which comprises the composition for dermal application according to any of claims 1 to 9.

17. A bath salt composition

which comprises the composition for dermal application according to any of claims 1 to 9.

18. A method for the treatment of skin diseases

which comprises applying, to a patient suffering from a skin disease, the therapeutic composition for skin diseases according to any of claims 10 to 14.

19. A method for the treatment of skin diseases

which comprises applying, to a patient suffering from a skin disease, a therapeutic agent for skin diseases other than the oxidized coenzyme Q represented by the formula (1) and other than the reduced coenzyme Q represented by the formula (2) in parallel with a therapeutic composition for skin diseases according to any of claims 10 to 14.

* * * * *

REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978
APPLICATION FOR A PATENT AND KNOWLEDGEMENT OF RECEIPT
(Section 30(1) Regulation 22)

FORM P.1
(to be lodged in duplicate)

THE GRANT OF A PATENT IS HEREBY REQUESTED BY THE UNDERMENTIONED APPLICANT ON THE BASIS OF THE PRESENT APPLICATION FILED IN DUPLICATE

21	PATENT APPLICATION NO	2001/9877	A&A REF	144857

71	FULL NAME(S) OF APPLICANT(S)

TECHNIKON PRETORIA

ADDRESS(ES) OF APPLICANT(S)

Staatsartilerie Road, Pretoria, 0002, Republic of South Africa

54	TITLE OF INVENTION

A NUTRITIONAL AND PHARMACEUTICAL COMPOSITION

Only the items marked with an "X" in the blocks below are applicable.

[X] THE APPLICANT CLAIMS PRIORITY AS SET OUT ON THE ACCOMPANYING FORM P.2. The earliest priority claimed is
Country: **ZA** No: **2000/4688** Date: **6 September 2000**

[ ] THE APPLICATION IS FOR A PATENT OF ADDITION TO PATENT APPLICATION NO 21 01

[ ] THIS APPLICATION IS A FRESH APPLICATION IN TERMS OF SECTION 37 AND BASED ON APPLICATION NO 21 01

THIS APPLICATION IS ACCOMPANIED BY:

- [X] Two copies of a complete specification of **26** pages
- [ ] Drawings of sheets
- [X] Publication particulars and abstract (Form P.8 in duplicate) (for complete only)
- [ ] A copy of Figure of the drawings (if any) for the abstract (for complete only)
- [X] An assignment of invention
- [ ] Certified priority document(s). (State quantity)
- [ ] Translation of the priority document(s)
- [ ] An assignment of priority rights
- [X] A copy of Form P.2 and the specification of RSA Patent Application No 21 01 **2000/4688**
- [X] Form P.2 in duplicate
- [X] A declaration and power of attorney on Form P.3
- [ ] Request for ante-dating on Form P.4
- [ ] Request for classification on Form P.9
- [ ] Request for delay of acceptance on Form P.4
- [ ] Extra copy of informal drawings (for complete only)

74	ADDRESS FOR SERVICE: Adams & Adams, Pretoria

Dated this 23 day of November 2001

ADAMS & ADAMS
APPLICANTS PATENT ATTORNEYS

The duplicate will be returned to the applicant's address for service as proof of lodging but is not valid unless endorsed with official stamp

OFFICIAL DATE STAMP

REGISTRAR OF PATENTS

A & A Ref No: **144857**

FORM P7

ADAMS & ADAMS
PATENT ATTORNEYS
PRETORIA

REPUBLIC OF SOUTH AFRICA
Patents Act, 1978

COMPLETE SPECIFICATION
(Section 30 (1) - Regulation 28)

21	01	OFFICIAL APPLICATION NO

2001/9677

22	LODGING DATE

23 NOVEMBER 2001

51	INTERNATIONAL CLASSIFICATION

A61K; A61P

71	FULL NAME(S) OF APPLICANT(S)

TECHNIKON PRETORIA

72	FULL NAME(S) OF INVENTOR(S)

LEHMANN, Susanna Maria Catrina

54	TITLE OF INVENTION

A NUTRITIONAL AND PHARMACEUTICAL COMPOSITION

THIS INVENTION relates to a nutritional and pharmaceutical composition, to a method of making a nutritional and pharmaceutical composition and to a non-therapeutic method of improving energy production in a person or animal.

According to a first aspect of the invention, there is provided a nutritional and pharmaceutical composition which includes at least one quinone coenzyme, at least one sugar, taurine, vitamin C, vitamin E, biotin and at least one B complex vitamin.

The quinone co-enzyme may be selected from 6-(10 hydroxyalkyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinones in which the hydroxyalkyl group is a C_7-C_{11} hydroxyalkyl group.

The quinone co-enzyme may thus be selected from 6-(10-hydroxyheptyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone,6-(10-hydroxyoctyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone, 6-(10-hydroxynonyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone, 6-(10-hydroxydecyl)-2,3-dimethoxy-5-methyl-1,4-

benzoquinone,6-(10-hydroxydodecyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone and mixtures thereof.

The sugar may be selected from glucose, fructose and mixtures thereof.

The Vitamin C may include ascorbic acid and its derivatives. The Vitamin E may be in the form of tocopherol acetate.

The B complex vitamin may be selected from thiamin (Vitamin B1) and its derivatives, riboflavin (Vitamin B2) and its derivatives, nicotinamide (niacin) (Vitamin B3) and its derivatives, pyridoxine (Vitamin B6) and its derivatives, pantothenic acid (Vitamin B5) and its derivatives, folic acid (Vitamin Bc) and its derivatives, cyanocobalamin (Vitamin B12) and its derivatives, carnitine (Vitamin Bt) and its derivatives, 1-mandelonitrile-β-glucoronic acid, (Vitamin B17) (amygdalin) and mixtures thereof.

The composition may include at least one further component selected from S-adenosylmethionine, myoinositol, β-carotene, N-acetylcysteine, methylsulphonylmethane, N,N-dimethylglycine (DMG), β-hydroxy-β-methylbutyrate (HMB), calcium, potassium and magnesium aspartate, malic acid and salts thereof lipoic acid and derivatives thereof, lactarin, methylcellulose, pectin, flavourants, potassium chloride, zinc chloride, magnesium chloride, glycerophosphate salts,

bilberry extract, and mixtures thereof.

The composition may include at least one of a betaine (trimethylglycine) or a derivative of a betaine.

The composition may, further, include a preservative. The preservative may be sodium benzoate or benzoic acid.

The composition may be in a form selected from a dry powder, a compressed tablet and an aqueous solution.

A preferred embodiment of the invention includes the components and quantities set out in Table 1.

TABLE 1

6-(10-hydroxyheptyl)-2-3 dimethoxy-5-methyl-1,4-benzoquinone	15 - 360 mg
6-(10-hydroxyoctyl)-2-3 dimethoxy-5-methyl-1,4-benzoquinone	15 - 360 mg
6-(10-hydroxynonyl)-2-3 dimethoxy-5-methyl-1,4-benzoquinone	15 mg - 360 mg
6-(10-hydroxydectyl)-2-3 dimethoxy-5-methyl-1,4-benzoquinone	15 mg - 360 mg
6-(10-hydroxydodecyl)-2-3 dimethoxy-5-methyl-1,4-benzo quinone	15 mg - 360 mg
taurine	15 mg - 360 mg
glucose	3 - 10% (m/m)
fructose	7 - 15% (m/m)
ascorbic acid	100 mg - 500 mg
thiamin	1 mg - 4 mg
riboflavin	2 mg - 5 mg
niacin	15 mg - 25 mg
pyridoxine	3 mg - 5 mg
cyanocobalamin	5 - 10 μg
biotin	0.3 mg - 3 mg
pantothenic acid	5 mg - 15 mg
tocopherol	15 mg - 30 mg
folic Acid	1 mg - 20 mg
carnitine	100 mg - 10,000 mg
myoinositol	4 mg
β-carotene	100 mg - 250 mg
1-mandelonitrile-β-glucuronic acid	50 mg - 300 mg

N-acetylcysteine	200 mg - 10,000 mg
HMB	150 mg - 500 mg
lipoic acid	200 mg - 2000 mg
sodium benzoate or benzoic acid	20 mg - 200 mg
calcium or potassium or magnesium aspartate	50 mg - 5000 mg
glycerophosphate salts	100 mg - 1000 mg
betaine	50 mg - 1000 mg
malic acid or salts thereof	50 mg - 1000 mg
bilberry extract	50 mg - 1000 mg

Preferably, the total of the quinone coenzymes in the composition will not exceed 720 mg.

A more preferred embodiment of the invention, includes the components and quantities set out in Table 2.

TABLE 2

6-(10-hydroxyheptyl)-2-3 dimethoxy-5-methylbenzoquinone	100 mg
6-(10-hydroxyoctyl)-2-3 dimethoxy-5-methyl-1,4-benzoquinone	100 mg
6-(10-hydroxynonyl)-2-3 dimethoxy-5-methyl-1,4-benzoquinone	100 mg
6-(10-hydroxydecyl)-2-3 dimethoxy-5-methyl-1,4-benzoquinone	100 mg
6-(10-hydroxydodecyl)-2-3 dimethoxy-5-methyl-1,4-benzoquinone	360 mg
taurine	200 mg
glucose	17500 mg
fructose	22500 mg
ascorbic acid	250 mg
thiamin	3 mg
riboflavin	5 mg
niacin	20 mg
pyridoxine	5 mg
cyanocobalamin	10μg
biotin	2 mg
pantothenic acid	15 mg
tocopherol	20 mg
folic acid	10 mg
carnitine	500 mg
myoinositol	3,5 mg
β-carotene	150 mg
1-mandelonitrile-β-glucuronic acid	100 mg

N-acetylcysteine	500 mg
lipoic acid	200 mg
sodium benzoate/benzoic acid	200 mg
calcium/potassium/magnesium aspartate	1000 mg
glycerophosphate salts	500 mg
betaine	500 mg
malic acid	500 mg
bilberry extract	800 mg

The composition may be provided in the form of three premixtures which may then be combined in a predetermined ratio in order to form the composition.

The invention thus extends to a three part kit for forming a nutritional and pharmaceutical formulation as hereinbefore described, each part comprising a premixture, the components of the premixtures being selected so that, by combining the components in a predetermined ratio the composition is formed.

The first premixture may include the quinone coenzymes, potassium, magnesium and zinc chloride, thiamin, riboflavin, nicotinamide, pyridoxine, biotin, folic acid, cyanocobalamin, β-carotene, lactarin, tocopherol, myoinositol, pantothenic acid, methylcellulose, pectin, ascorbic acid and glycerophosphate salt.

The second premixture may include carnitine, N -acetylcysteine, methylsulphonylemethane, β-hydroxy-β-methylbutyrate, calcium/potassium/magnesium aspartate and sodium benzoate.

The third premixture may include 1-mandelonitrile- β-glucuronic acid, the N,N-dimethylglycine, betaine, malic acid, bilberry extract and lipoic acid.

Thus, the first premixture may include components selected from quinone coenzymes, potassium, chloride, magnesium chloride, zinc chloride, thiamin, riboflavin, nicotinamide, pyridoxine, biotin, folic acid, cyanocobalamin, β-carotene, lactarin, tocopherol, myoinositol, pantothenic acid, methylcellulose, pectin, ascorbic acid and glycerophosphate salt, the second premixture may include components selected from carnitine, N -acetylcysteine, methylsulphonylemethane, β-hydroxy-β-methylbutyrate, calcium or potassium or magnesium aspartate and sodium benzoate and the third premixture may include components selected from 1-mandelonitrile-β-glucuronic acid, N,N-dimethylglycine, betaine, malic acid, bilberry extract and lipoic acid.

The amounts of each of the components of the premixtures will be selected so that, when the premixtures are combined in a predetermined ratio, either in a dry powder form or in solutions having predetermined concentrations, a dry powder composition or a solution in which the components are present in the quantities as set out in Tables 1 or 2 will be produced.

According to another aspect of the invention, there is provided a method of making a nutritional and pharmaceutical composition, the method including the step of combining at least one quinone coenzyme, at least one sugar, taurine, vitamin C, vitamin E, biotin, betaine and B complex vitamins to form the composition.

The quinone coenzyme, the sugar and the B complex vitamins may be as hereinbefore described.

According to another aspect of the invention, there is a provided a method of making a three part kit for forming a nutritional and pharmaceutical composition as hereinbefore described, the method including the step of separately combining components selected from quinone coenzymes as hereinbefore described, sugars as hereinbefore described, taurine, Vitamin C, the B complex vitamins as hereinbefore described, the further components as hereinbefore described, a betaine or a derivative of a betaine, and a preservative to form three separate compositions such that, by combining predetermined amounts of the three compositions, the nutritional and pharmaceutical composition is produced.

In a preferred embodiment of the invention the components as set out in Table 1 are combined in the amounts set out in Table 1. In a more preferred embodiment of the invention the components set out in Table 2 are combined in the amounts set out in Table 2.

The method may include preparing premixtures as hereinbefore described.

The invention extends to a non-therapeutic method of improving energy production in a person or animal, the method including administering a composition as hereinbefore described to the person or animal.

The dosage may be between 50 - 150g over a period of 24 hours in divided doses.

The invention is now described, by way of example, with reference to the accompanying Example.

EXAMPLE 1

A first premixture was prepared by mixing

6-(10-hydroxyheptyl)-2-3 dimethoxy-5-methylbenzoquinone	360 mg
6-(10-hydroxyoctyl)-2-3 dimethoxy-5-methylbenzoquinone	360 mg
6-(10-hydroxynonyl)-2-3 dimethoxy-5-methyl-1,4-benzoquinone	360 mg
6-(10-hydroxydecyl)-2-3 dimethoxy-5-methyl-1,4-benzoquinone	360 mg

6-(10-hydroxydodecyl)-2-3 dimethoxy-5-methyl-1,4-benzoquinone	360 mg
potassium chloride	500 mg
magnesium chloride	250 mg
zinc chloride	75 mg
thiamin	23 mg
riboflavin	16 mg
niacin	78 mg
pyridoxine	8 mg
biotin	3 mg
folic acid	40 mg
cyanocobalamin	10mg
β-carotene	200 mg
lactarin	780 mg
tocopherol	20 mg
myoinositol	4 mg
pantothenic acid	15 mg
sodium benzoate	2 mg
methyl cellulose	300 mg
pectin	300 mg
ascorbic acid	1000 mg
glycerophosphate salt	500 mg
glucose	17500 mg
fructose	25000 mg

A second premixture was prepared by mixing

carnitine	500 mg
N-acetylcysteine	500 mg
methyl sulfonylmethane	1000 mg
HMB	200 mg
sodium benzoate/benzoic acid	200 mg
ornithine	500 mg
calcium/potassium/magnesium aspartate	200 mg
taurine	200 mg

A third premixture was prepared by mixing

bilberry extract	800 mg
1-mandelonitrile-β-glucoronic acid	100 mg
N,N-dimethylglycine	100 mg
lipoic acid	600 mg
betaine	500 mg
malic acid	500 mg

In order to prepare the composition, the first premixture was added to water (200 mℓ) and thoroughly mixed until the components of the premixture had dissolved or suspended to produce a first premixture suspension. The second premixture was added to water (200 mℓ) and thoroughly mixed until the components had dissolved or suspended to form a second premixture suspension. The first and second premixture suspensions were combined and mixed for 10 minutes in a mixer. The third premixture was added to the

combined first and second premixture suspensions and the resulting mixture mixed for about 5 minutes. Water (2 ℓ) was then added and mixed well for 20 minutes to produce a concentrate.

For the dry powder and compressed pills all the ingredients were mixed without any water.

The composition of the invention was used to improve energy production in marathon runners, cancer sufferers, sports players such as tennis players, badminton players, rugby players, AIDS patients, chronic fatigue syndrome patients and people suffering from stress.

The invention is now illustrated, by way of example, with reference to the following dosages and test results.

Dosages:

In the case of tablets, 1 - 10 may be taken by mouth per day but at least 1 ℓ of water should also be ingested.

In the case of the dry powder, 4 teaspoons may be dissolved in 500 m ℓ of water and taken at least 1 hour before exercising or during the day.

The concentrate should be diluted (1 part concentrate in 3 parts water) before

ingestion. The dosage is about 200 - 300 mℓ twice per day or as needed but preferably not more than 1 ℓ per day. In the case of sportsmen and women and athletes a dosage should be taken about 1 hour before exercising.

Test Results

A group of ten marathon runners, aged between 19 and 62 were given the composition of the invention and improved their best time for running a marathon by between 20 and 45 minutes. The total time to full recovery was also much shorter. Cancer patients given the composition of the invention had more energy and showed reduced negative side effects from chemotherapy (less nausea, better appetite).

In another test, 487 people complaining of tiredness were given the composition. Of this group, 485 reported a significant improvement in their energy levels.

The invention is the result of research with people with mitochondrial defects, chronic fatigue and fibromyalgesia. This regime can also be personalized after metabolic status assessment through various analyses of blood, urine, saliva and CSF (cerebrospinal fluid) for specific metabolic compounds.

It is an advantage of the invention illustrated that the composition serves to eliminate or reduce cell damaging substances before damage can be done. The composition also provides the substrates for optimal energy processes. The composition also enhances endurance by optimizing the mitocondrial processes and protection of cells.

The metabolic enhancer contains various anti-oxidants and cell membrane protectors that scavenge the oxidative (free radicals) byproducts of energy formation reactions before damage can be done (e.g. $OH^{\cdot}$; $O^{\cdot}_3$; H_2O_2 and many more).

The composition supplies the cells with necessary nutrients that complement one another in the formation of energy.

Endurance depends to a large degree on the available compounds to produce energy and the concentration of the byproducts formed during the energy process. The metabolic enhancer supplies the substances needed for energy production but also eliminates waste products which are formed and which can harm the cells and thus organs. The unique formulation of the composition supplies the user with natural compounds that can readily and directly be utilised by the cell. The compounds are in a form such that chemical or enzymatic breakdown before utilization is not necessary. All of the compounds are directly incorporated into the metabolism. All cell energy

processes are enhanced.

The anti-oxidants in the formulation remove waste products formed during the energy producing process before damage can be done to the cell and cell organelles membranes. The metabolic enhancer will also take the user to a level of preventative health care because cells will function nearer to the optimum.

The enhancer contains no banned substances such as caffeine or ephedrine.

CLAIMS:

1. A nutritional and pharmaceutical composition which includes at least one quinone coenzyme, at least one sugar, taurine, vitamin C, vitamin E, biotin and at least one B complex vitamin.

2. A composition as claimed in Claim 1, in which the quinone co-enzyme is selected from 6-(10-hydroxyalkyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinones in which the hydroxyalkyl group is a C_7-C_{11} hydroxyalkyl group.

3. A composition as claimed in Claim 2, in which the quinone co-enzyme is selected from 6-(10-hydroxyheptyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone,6-(10-hydroxyoctyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone, 6-(10-hydroxynonyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone, 6-(10-hydroxydecyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone,6-(10-hydroxydodecyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone and mixtures of any two or more thereof.

4. A composition as claimed in any one of the preceding claims, in which the sugar is selected from glucose, fructose and mixtures thereof.

5. A composition as claimed in any one of the preceding claims, in which the Vitamin E is in the form of tocopherol acetate.

6. A composition as claimed in any one of the preceding claims, in which the B complex vitamin is selected from thiamin (Vitamin B1) and its derivatives, riboflavin (Vitamin B2) and its derivatives, nicotinamide (niacin) (Vitamin B3) and its derivatives, pyridoxine (Vitamin B6) and its derivatives, pantothenic acid (Vitamin B5) and its derivatives, folic acid (Vitamin Bc) and its derivatives, cyanocobalamin (Vitamin B12) and its derivatives, carnitine (Vitamin Bt) and its derivatives, 1-mandelonitrile-β-glucoronic acid, (Vitamin B17) (amygdalin) and mixtures of any two or more thereof.

7. A composition as claimed in any one of the preceding claims, which includes at least one further component selected from S- adenosylmethionine (stabilised), myoinositol, β-carotene, N-acetylcysteine, methylsulphonylmethane, N,N-dimethylglycine (DMG), β-hydroxy-β-methylbutyrate (HMB), calcium aspartate, potassium aspartate, magnesium aspartate, malic acid, salts of malic acid, salts of lipoic acid, derivatives of lipoic acid, lactarin, methylcellulose, pectin, flavourants, potassium chloride, zinc chloride, magnesium chloride, glycerophosphate salts, bilberry extract and mixtures of any two or more thereof.

8. A composition as claimed in any one of the preceding claims, which includes at least one of a betaine (trimethylglycine) or a derivative of a betaine.

9. A composition as claimed in any one of the preceding claims which includes a preservative.

10. A composition as claimed in any one of the preceding claims, which is in a form selected from a dry powder, a compressed tablet and an aqueous solution.

11. A composition as claimed in any one of the preceding claims which has the following composition:

6-(10-hydroxyheptyl)-2-3 dimethoxy-5-methyl-1,4-benzoquinone	15 - 360 mg
6-(10-hydroxyoctyl)-2-3 dimethoxy-5-methyl-1,4-benzoquinone	15 - 360 mg
6-(10-hydroxynonyl)-2-3 dimethoxy-5-methyl-1,4-benzoquinone	15 mg - 360 mg
6-(10-hydroxydectyl)-2-3 dimethoxy-5-methyl-1,4-benzoquinone	15 mg - 360 mg
6-(10-hydroxydodecyl)-2-3 dimethoxy-5-methyl-1,4-benzo quinone	15 mg - 360 mg
taurine	15 mg - 360 mg
glucose	3 - 10% (m/m)
fructose	7 - 15% (m/m)
ascorbic acid	100 mg - 500 mg
thiamin	1 mg - 4 mg
riboflavin	2 mg - 5 mg
niacin	15 mg - 25 mg
pyridoxine	3 mg - 5 mg
cyanocobalamin	5 - 10 μg
biotin	0.3 mg - 3 mg
pantothenic acid	5 mg - 15 mg

tocopherol	15 mg - 30 mg
folic Acid	1 mg - 20 mg
carnitine	100 mg - 10,000 mg
myoinositol	4 mg
β-carotene	100 mg - 250 mg
1-mandelonitrile-β-glucuronic acid	50 mg - 300 mg
N-acetylcysteine	200 mg - 10,000 mg
HMB	150 mg - 500 mg
lipoic acid	200 mg - 2000 mg
sodium benzoate or benzoic acid	20 mg - 200 mg
calcium or potassium or magnesium aspartate	50 mg - 5000 mg
glycerophosphate salts	100 mg - 1000 mg
betaine	50 mg - 1000 mg
malic acid or salts thereof	50 mg - 1000 mg
bilberry extract	50 mg - 1000 mg

12. A composition as claimed in Claim 11 which has the following composition:

6-(10-hydroxyheptyl)-2-3 dimethoxy-5-methylbenzoquinone	100 mg
6-(10-hydroxyoctyl)-2-3 dimethoxy-5-methyl-1,4-benzoquinone	100 mg
6-(10-hydroxynonyl)-2-3 dimethoxy-5-methyl-1,4-benzoquinone	100 mg
6-(10-hydroxydecyl)-2-3 dimethoxy-5-methyl-1,4-benzoquinone	100 mg

6-(10-hydroxydodecyl)-2-3 dimethoxy-5-methyl-1,4-benzoquinone	360 mg
taurine	200 mg
glucose	17500 mg
fructose	22500 mg
ascorbic acid	250 mg
thiamin	3 mg
riboflavin	5 mg
niacin	20 mg
pyridoxine	5 mg
cyanocobalamin	10μg
biotin	2 mg
pantothenic acid	15 mg
tocopherol	20 mg
folic acid	10 mg
carnitine	500 mg
myoinositol	3,5 mg
β-carotene	150 mg
1-mandelonitrile-β-glucuronic acid	100 mg
N-acetylcysteine	500 mg
lipoic acid	200 mg
sodium benzoate or benzoic acid	200 mg
calcium or potassium or magnesium aspartate	1000 mg
glycerophosphate salts	500 mg
betaine	500 mg
malic acid	500 mg
bilberry extract	800 mg

13. A three part kit for forming a composition as claimed in any one of the preceding claims, each part comprising a premixture, the components of the premixtures being selected so that, by combining the components in a predetermined ratio the composition is formed.

14. A kit as claimed in Claim 13, in which the first premixture includes components selected from quinone coenzymes, potassium, chloride, magnesium chloride, zinc chloride, thiamin, riboflavin, nicotinamide, pyridoxine, biotin, folic acid, cyanocobalamin, β-carotene, lactarin, tocopherol, myoinositol, pantothenic acid, fructose, methylcellulose, pectin, ascorbic acid and glycerophosphate salt, the second premixture includes components selected from taurine, carnitine, N-acetylcysteine, methylsulphonylemethane, β-hydroxy-β-methylbutyrate, calcium or potassium or magnesium aspartate and sodium benzoate and the third premixture includes components selected from 1-mandelonitrile- β-glucuronic acid, N,N-dimethylglycine, betaine, malic acid, bilberry extract and lipoic acid.

15. A method of making a nutritional and pharmaceutical composition, the method including the step of combining at least one quinone coenzyme, at least one sugar, taurine, vitamin C, vitamin E, biotin and at least one B complex vitamin to form the composition.

16. A method as claimed in Claim 15, in which the quinone coenzyme is

as set out in Claim 2.

17. A method as claimed in Claim 16, in which the quinone coenzyme is as set out in Claim 3.

18. A method as claimed in any one of Claims 15 to 17 inclusive, in which the sugar is set out in Claim 4.

19. A method as claimed in any one of Claims 15 to 18 inclusive, in which the Vitamin E is as set out in Claim 5.

20. A method as claimed in any one of Claims 15 to 19 inclusive, in which the B complex vitamins are as set out in Claim 6.

21. A method of making a three part kit for forming a nutritional and pharmaceutical composition as claimed in any one of Claims 1 to 12 inclusive, the method including the step of separately combining components selected from the quinone coenzymes of Claim 3, the sugar of Claim 4, taurine, Vitamin C, the B complex vitamins of Claim 6, the further components of Claim 7, a betaine or a derivative of a betaine, and a preservative to form three separate compositions such that, by combining predetermined amounts of the three compositions, the nutritional and pharmaceutical composition is produced.

22. A non-therapeutic method of improving energy production in a person or animal, the method including administering to a person or animal a composition as claimed in any one of Claims 1 to 12 inclusive.

23. A method as claimed in Claim 22, in which the dosage is between 50 and 150 g over a period of 24 hours in divided doses.

24. A composition as claimed in Claim 1, substantially as herein described and illustrated.

25. A kit as claimed in Claim 13, substantially as herein described and illustrated.

26. A method of making a composition as claimed in Claim 15, substantially as herein described and illustrated.

27. A method of making a kit as claimed in claim 21, substantially as herein described and illustrated.

28. A non-therapeutic method as claimed in Claim 22, substantially as herein described and illustrated.

29. A new composition, a new kit, a new method of making a

composition, a new method of making a kit or a new non-therapeutic method substantially as herein described.

DATED THIS 23RD DAY OF NOVEMBER 2001

ADAMS & ADAMS
APPLICANTS PATENT ATTORNEYS